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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request f r filing a PROVISIONAL APPLICATION FOR PATENT und r 37 CFR 1.53 (c).

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TITLE OF THE INVENTION (280 characters max)

Chlamydia Antigens and Corresponding DNA Fragments and Uses Thereof

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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Respectfully submitted,

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS

Cross reference is made to U.S. patent application Serial Number 09/106,684 filed June 29, 1998, to international application Serial Number PCT/US97/19651 and U.S. Patent application serial number 08/957,485, both filed October 24, 1997, and to U.S. Provisional patent application serial Number 60/029,120 filed Oct. 24, 1996, all incorporated herein by reference.

The present invention is directed to transdermal administration of pharmacologic agents, especially psychopharmacologic agents including citalopram, such as using a gel matrix, preferably a lecithin organogel and/or a polymer gel.

BACKGROUND INFORMATION

Recently, and particularly over the last fifteen years or so, patients suffering from a wide variety of conditions have been successfully treated by administration of psychopharmacologic or psychotropic agents. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such psychopharmacologic agents has been infeasible or ineffective. In some cases, oral administration is associated with side effects, particularly gastrointestinal side effects, which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparation have resulted in subtherapeutic plasma levels. In other cases, the psychopharmacologic agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the pharmaceutical is absorbed via the digestive system before entering the bloodstream. A number of psychopharmacologic agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular tissue to achieve desired results. Oral or injection administration of psychopharmacologic agents may result in to slow or too rapid increase in blood plasma levels, e.g. may involve an undesirably long time delay as the pharmaceutical is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasmal levels followed by an undesirably low level, where a more

constant level would be preferable. Some pharmaceuticals are particularly prone to cause or contribute to liver damage when administered orally.

One alternative route of administration for selected pharmaceuticals, has been transdermal delivery. Transdermal delivery has been utilized, e.g., for the treatment of high blood pressure, for ischemic heart disease and for hormone replacement. Transdermal delivery is not necessarily appropriate for all types of pharmaceuticals and, it is believed, has not, in general, previously been successfully used, with full effectiveness, for psychopharmacologic or psychotropic agents. Transdermal delivery is accompanied by its own side effects, including a potential for skin irritation, arising from the gel or other matrix, from the pharmaceutical itself, or from the interaction of the pharmaceutical with the matrix. Furthermore, a transdermal system must be configured such that the combination of the matrix and the pharmaceutical does not react with or modify the pharmaceutical, or otherwise render it ineffective, such that the combination provides sufficient diffusion coefficients, such that the delivery system is not adversely affected by expected temperature variations during normal use, such that the gel or other matrix retain the desired viscosity, and such that the pharmaceutical can be properly dispersed or dissolved in the matrix and the like.

Although other forms of delivery of psychopharmacologic and other pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with psychopharmacologic agents currently in use or with many other pharmaceuticals.

Accordingly, it would be useful to provide a transdermal delivery system effective to provide good transdermal absorption and acceptable plasma blood levels of psychotropic or psychopharmacologic agents, preferably a system which can be adapted for use with a wide variety of different psychopharmacologic agents for transdermal delivery of effective amounts of such agents at a desired or controlled rate, while preferably avoiding or reducing undesired effects such as liver damage.

SUMMARY OF THE INVENTION

The present invention provides for transdermal delivery of pharmacologic agents, particularly psychopharmacologic agents, by dissolving or dispersing such agents in a gel, preferably a lecithin organogel. In one embodiment, citalopram is delivered using a lecithin gel such as a gel formed using lecithin and an organic solvent such as ethoxy diglycol. In one embodiment, the gel includes or is formed from a polymer such as that sold under the trade name "Pluronic" available from BASF-Wyandotte Corporation, Parsippany, New Jersey.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment of the invention, a gel containing citalopram HBR (sold under the trade name Celexa) is formed. The citalopram may be mixed in a material such as ethoxy diglycol and/or ethanol (although ethanol evaporates more quickly which may result in the citalopram being less well absorbed). The mixture is added to a gel formed from lecithin and Pluronic. Application to the skin of a human is believed to be substantially without skin irritation, and to result in transdermal delivery of a therapeutically effective dose of citalopram, while avoiding certain side effects, such as gastrointestinal side effects, like nausea and/or stomach pain that are sometimes associated with oral delivery of citalopram.

One class of psychopharmacologic agents, some of whose members can be administered according to embodiments of the present invention, are serotonin specific reuptake inhibitors (SSRIs). SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox). Although many patients tolerate oral administration of these SSRIs, a certain population of patients experience gastrointestinal side effects. Without wishing to be bound by any theory, it is believed that such side effects may be relatively frequent for SSRIs in part because the gastrointestinal system is richly endowed with serotonin receptors and that SSRIs may result in such side effects as

alterations in gastric motility, nausea, and diarrhea. Medically healthy individuals may tolerate oral dosing with SSRIs with difficulty, or not at all. Medically compromised patients, for example patients with gastric or duodenal ulcer, ulcerative colitis, irritable colon syndrome or regional enteritis may not be able to tolerate the oral form of these medications and thus, in the absence of alternative administration routes, may be deprived of helpful antidepressant pharmacotherapeutic treatment.

Another class of psychopharmacologic agents which may be administered accordingly to embodiments of the present invention include antidepressants such as buproprion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Tegretol), nefazodone (sold under the trade name Serzone) and trazadone (sold under the trade name Desyrel). Although these antidepressant medications are often well tolerated by the gastrointestinal (GI) system, in some cases, oral preparations have resulted in malabsorption problems or idiosyncratic side effects, which, in some cases, may be avoided by transdermal administration according to embodiments of the present invention, as described more thoroughly below.

Yet another category of psychopharmacologic agents are mood stabilizing medications, examples of which include carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. Many patients have difficulty tolerating the gastrointestinal side effects of these medications, most typically nausea. Such side effects are particularly troublesome for these agents since compliance with rigorously regular medication schedules is of great clinical importance to many of these patients. Accordingly, transdermal delivery according to embodiments of the present invention is particularly helpful in achieving compliance with a regular medication schedule.

Another type of psychopharmaceutical agent are those used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is permoline, sold under the trade name Cylert. Permoline is a medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in children and adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration. Its principal problem in

medical practice is its association with chemical hepatitis (hepatotoxicity). Since approximately 80% of orally ingested pemoline goes through the liver prior to reaching the bloodstream (called first pass metabolism), transdermal administration, which bypasses the liver, may offer a significant advantage in reducing liver metabolism. It is anticipated that the incidence of chemical hepatitis might be significantly lower for transdermally administered permoline.

Another type of psychopharmaceutical agent includes dopamine agents, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel. Oral administration of dopamine agents such as pergolide or bromocriptine mesylate may be sub-optimal because of GI irritation. Accordingly, transdermal delivery of dopamine agents such as pergolide and bromocriptine mesylate, according to embodiments of the present invention, is particularly useful.

Another type of psychopharmaceutical agent are those used for treating depression and/or chronic pain, one example of which is amitriptylene, sold under the trade name Elavil. Oral administration of amitriptylene may be sub-optimal when high local tissue concentrations are desired. Accordingly, transdermal delivery of amitriptylene, according to embodiments of the present invention, is particularly useful.

Another type of psychopharmaceutical agent are those used for treating hypertension and akathisia, one example of which is propanalol, sold under the trade name Inderol. Oral administration of propanalol may be sub-optimal because of rare GI intolerance or malabsorption. Accordingly, transdermal delivery of propanalol according to embodiments of the present invention is particularly useful.

Another type of pharmaceutical that may be particularly useful for localizing the dosage via transdermal applications are anticonvulsant/antispasmodic agents such as gabapentin (sold under the trade name Neurontin, an anticonvulsant medication that may also act as an antispasmodic agent. With relief of spasms, some pain relief is often experienced. In oral form, gabapentin is finding particular application in patients who have some neurologic component to cervical, thoracic, or low back pain. Transdermal application of gabapentin is expected to be a particularly effective means of obtaining higher local concentrations of the medication. The

combinations described in some of the examples below are means of adding to the antispasmodic and analgesic properties of the gabapentin.

According to embodiments of the present invention, tablets, capsules or other preparations of psychopharmacologic agents or other pharmaceuticals, e.g., intended for oral delivery, were crushed and dispersed or dissolved in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate. In some cases, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water was formed.

Without wishing to be bound by any theory, it is believed the degree to which pharmaceutical compounds will successfully diffuse or be transdermally transported through the skin into blood vessels is related in part to properties of lipid solubility. Lipid solubilities of pharmaceuticals are, to some extent, inversely proportional to their aqueous solubility, which is in part a function of the compound's polarity. Therefore, fluoxetine hydrochloride, which has limited aqueous solubility and apparent moderate lipid solubility, is transdermally transported whereas venlafaxine and buproprion, it is currently believed, are not transported particularly effectively. The oil-water coefficient is believed to be partially predictive of the degree to which a given compound, theoretically, can be transdermally transported. However, because the physical properties of these complex organic compounds are neither fully determined nor documented and because other factors may be significant, (any some of which are understood) it is not possible, to predict, other than in approximate general terms, their potential for (and thus the advisability of testing for) transdermal transport. These physical properties are particularly complex and difficult to forecast, e.g., because of the molecular mechanical release and retention properties of organogel lecithin, which contains a very long chain polymer (Pluronic) that has been demonstrated to vary widely, e.g., with temperature, percentage composition of the gel, and concentration of the pharmaceutical.

Detailed examples of the preparation are provided below, along with examples of results obtained or expected from transdermal administration to human patients. Typically, the gel preparation was or will be applied to the upper arm of the patient covering a surface of approximately 20 square centimeters. Laboratory measures of plasma blood levels were or will be obtained as shown in the examples below. The results generally demonstrate or are expected

to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Some patients were or will be evaluated by means of a structured evaluation form, completed at a frequency of at least one time per week. Patients were or will be evaluated both for all the present symptoms as well as any side effects from currently administered medications. This is believed to make it possible to note changes on an ongoing basis. In general, for psychiatric patients, those with the most clear cut and uncomplicated diagnoses of major depression experienced, or are expected to experience, the best results. Patients with severe personality disorders or with concealed substance abuse disorders generally did less well.

Experimental

Example 1

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency is formed.

Example 3

A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24

hours. The resulting 100 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

Example 3A

280 mg of Citalopram HBr was crushed and strained and placed in a syringe with 1 cc of ethoxy diglycol. The combination was mixed well between two syringes. 3ml of Soya Lecithin was added and mixed well. Sufficient Pluronic F127 was added to the gel to produce a volume of 14 mL, and mixed well to produce a gel having a strength of about 20 mg citalopram per mL of gel.

Example 3B

280 mg of Citalopram HBr was crushed and strained and placed in a syringe with 1 cc of 95% ethanol. The combination was mixed well between two syringes. 3ml of Soya Lecithin was added and mixed well. Sufficient Pluronic F127 was added to the gel to produce a volume of 14 mL, and mixed well to produce a gel having a strength of about 20 mg citalopram per mL of gel.

Example 3C

2 cc of the gel of Example 3A was applied in the post auricular region by a 40-year-old male with a diagnosis of major depressive episode, severe. The patient had, in the past, responded to oral citalopram with marked improvement of his mood, but developed severe gastrointestinal side effects, with nausea and stomach pain. The transdermal citalopram was less immediate in its antidepressant effect, but the patient displayed steady improvement as the citalopram was transdermally administered over a period of five days. The citalopram gel produced no gastrointestinal side effects and no skin irritation.

Example 4

Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of

soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

Example 5

Sixty 100 milligram tablets of buproprion were ground and strained to form a fine powder. The buproprion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the buproprion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the buproprion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of buproprion HCl organogel having a strength of 15 milligrams per milliliter.

Example 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C, to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was

disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

Example 7

Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

Example 8

Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the

cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using

another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

Example 12

Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49 ± 26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

Example 13

Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30-200 mg/mL indicating possible limited absorption or lab error.

Example 14

Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of Prozac was determined to be 45/45 ng/mL, while typical reference levels are 50-480 ng/mL indicating good absorption. There was evidence of patient benefit from the clinical evaluation.

Example 15

Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μg) per mL , while typical therapeutic levels are 4-10 μg/mL indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 μg/mL, while typical therapeutic levels are 4-10 μg/mL indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL, while typical reference levels are 30-200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

Example 18

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 μg/mL, while

typical therapeutic levels are 4-10 μg/mL, indicating poor absorption, lab error, or patient non-compliance.

Example 19

Buproprion is highly soluble in water. Buproprion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10-30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

Fluoxetine gel was prepared, according to the procedures of example 6.. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20mg and 200 mg, more preferably between about 20 mg and about 160 mg, more preferably about 80 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20-60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30-180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg per day was self-administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine

and 25 ng/mL norfluoxetine, while typical reference levels are 50-480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

Example 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg/day was self administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50-200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7-90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200-400 mg per day was self-administered by 6 patients, including those of examples

14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side-effects were reported. The clinical evaluation of the patients over a 30-300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30-210 day period of such transdermal administration indicated moderate clinical improvement of depression.

Example 26

Five 150 mg tablets of amitriptylene were crushed and run through a strainer. The powder was put into syringes with a Luer-Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30 mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 23. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

Trazadone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50-150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42-90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150-225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15-165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

Example 30

Propanalol (Inderol) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propanalol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 31

Buproprion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150-200 mg per day was self-administered by 3 patients, including that of

example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5-45 day period of such transdermal administration indicated equivocal results.

Example 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500-1000 mg was self-administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Minimal skin irritation and no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months indicated a good response to treatment. After 28 days, blood was drawn and a serum valproic acid level of 26 µg/mL was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50-150 µg/mL. This indicated fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 µg/mL was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of buproprion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5-45 day period of such transdermal administration is expected to indicate a good response to treatment.

Example 35

Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

Example 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully with oral permoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, permoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin for a period of at least one hour. No skin irritation is expected. The clinical results are expected to be

comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered Fluoxetine, Valproic acid, Sertaline and Carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. The single laboratory measure of Paroxetine plasma level indicated poor absorption, laboratory error, or patient non-compliance. However, the patients' clinical response indicated positive medication effect. Both the laboratory measure of Buproprion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

Patients in the examples above were evaluated by means of a structured evaluation form depicted in Fig. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

Example 38

1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

Example 39

Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

Example 40

Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptylene.

Example 42

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%-6% will be combined with clonidine in concentrations between .2% and .3%.

Example 44

A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been

administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

In light of the above description, a number of advantages of the present invention can be seen. The present invention provides for psychopharmaceutical and other pharmaceutical treatment using a transdermal delivery system. The invention makes it possible to provide such treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention is able to achieve delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and have received clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally.

A number of variations and modifications of the invention can also be used. Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications. One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the

need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Although, in at least some of the embodiments described above, the pharmaceutical was provided by crushing and/or sieving tablets which include fillers or binders in addition to the pharmaceutical, the present invention can also be used by mixing, with the gel, the pharmaceutical in a relatively pure form, without filler. It is believed that this approach is likely to improve pharmaceutical delivery. In some embodiments, selected enzymes or other materials that act as transdermal delivery enhancers may be included. Carriers such as organogel lecithin matrix may be enhanced or replaced by, for example, reverse micelles (water and oil microemulsions) and/or lyposomes (lipid vesicles).

Although the present invention has been described by way of self-administered doses in the form of a gel applied to the skin by the patient, the present invention can also be implemented by providing the transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g. by placing the adhesive patch on the skin of the patient. Although the invention has been described in connection with positioning the psychopharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay speed duration, or rate of delivery of the pharmaceutical, either with respect to a particular tissue or systemically. For example, when a rapid rise in blood

serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nosedrops, eardrops, eyedrops and/or suppositories.

Although lecithin organogel has been described as a delivery matrix, other lecithin materials can be used including lecithin combined with Pluronic Gel, or Carbopol. Although the examples above describe a gel which combines lecithin organogel with a polymer gel such as Pluronic gel, lecithin gel can be provided without combining with Pluronic gel or may be combined with other gels such as Carbopol. Although in the above examples, pharmaceuticals were combined with gels to provide concentration such that an effective dose occupies between about 1 mL and about 2 mL, other ratios can be used to provide for larger or smaller volume of gel per effective dose. Although a lecithin or lecithin gel carrier is described, it is believed transdermal delivery of at least some of the prescribed pharmaceuticals can be achieved using other carriers, or without using any carrier. Unless otherwise noted, an effective dose refers to a mass or volume of fluoxetine delivered across the skin. Preferably, an effective dose is delivered to the target tissue or systemically in an amount or manner to achieve therapeutically helpful amounts or concentrations in the target tissue or systemically (such as indicated by a blood plasma level).

In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Although the application has been described by way of a preferred embodiment and certain variations and modifications, other variations and modification can also be used, the invention being defined by the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising:

an effective amount of a psychopharmaceutical composition;

lecithin organogel;

2. The composition of claim 1, wherein said psychopharmaceutical is selected from the group consisting of citalopram, sertraline, fluoxetine, carbamazepine, amitriptylene, trazadone, fluvoxamine, permoline, pergolide, bromocriptine mesylate, propanolol, buproprion, reboxetine, valproic acid, and nefazodone.

3. A method for preparing a composition for transdermal delivery of a psychopharmaceutical comprising:

preparing a first psychopharmaceutical in liquid or finely-divided form;

mixing said psychopharmaceutical with lecithin organogel;

4. A method for treatment of humans comprising:

preparing a composition comprising a psychopharmaceutical and lecithin organogel;

applying to the skin of said human a volume of said composition containing an effective dose of said psychopharmaceutical.

5. A composition comprising citalopram and lecithin in a gel form having a strength of 20 mg citalopram per mL of gel..

6. A composition, as claimed in claim 5, further comprising Pluronic F127.

7. A method for treatment of mammals comprising:

preparing a composition comprising a pharmaceutical in finely-divided or liquid form, wherein said pharmaceutical is selected from the group consisting of

citalopram,

fluoxetine,
buproprion,
reboxetine,
carbamazepine,
valproic acid,
sertraline,
fluvoxamine,
nefazodone,
trazadone,
amitriptylene,
propanolol,
permoline,
pergolide,
gabapentin, and
bromocriptine mesylate;

applying to a first region the skin of said mammal a volume of said composition containing an effective dose of said pharmaceutical wherein said effective dose is delivered transdermally.

8. A method, as claimed in claim 7, wherein said method is used for treatment of humans.

9. A method, as claimed in claim 7, wherein said composition further comprises lecithin.

10. A method, as claimed in claim 7, wherein said composition further comprises lecithin organogel.

11. A method, as claimed in claim 7, wherein said composition further comprises a transdermal transport enhancer.

12. A method, as claimed in claim 7, further comprising selecting said first region for application of said composition so as to enhance the rate of increase in plasma level of citalopram.

13. A method for treatment of humans comprising:

dissolving citalopram in a liquid solvent;

mixing said dissolved citalopram with lecithin, and Pluronic gel to form a therapeutic gel wherein the weight of citalopram per volume of therapeutic gel is about 20 mg per mL;

selecting a region of the skin of said human so as to increase the rate of increase in plasma level of citalopram, compared to at least one other area of the skin of said human, in response to application of said therapeutic gel to said region; and

applying said therapeutic gel to said region of the skin of said human.

14. A composition comprising citalopram and a gel in a ratio of about 20 mg ciralopram per mL of gel, said gel selected to permit transdermal delivery of an effective dose of citalopram in response to application to the skin of a human.

15. A composition comprising:

about 280 mg citalopram,

about 1 cc ethoxy diglycol,

about 2 mL soya lecithin, and

sufficient Pluronic gel to produce a volume of 14 mL.

16. A system for transdermal delivery of a pharmaceutical, comprising:

a pharmaceutical selected from the group consisting of:

citalopram,

fluoxetine,
buproprion,
reboxetine,
carbamazepine,
valproic acid,
sertraline,
fluvoxamine,
nefazodone,
trazadone,
amitriptylene,
propanolol,
permoline,
pergolide,
gabapentin, and
bromocriptine mesylate; and

means for providing transdermal delivery of said pharmaceutical when applied to human skin.

17. A system, as claimed in claim 16, wherein said means for providing transdermal delivery comprises lecithin.

18. A system, as claimed in claim 16, wherein said means for providing transdermal delivery comprises an organogel.

19. A system, as claimed in claim 16, wherein said means for providing transdermal delivery comprises an adhesive patch.

20. A product for transdermal delivery of a pharmaceutical made by a process which comprises mixing a pharmaceutical selected from the group consisting of

citalopram,
fluoxetine,
buproprion,
reboxetine,
carbamazepine,
valproic acid,
sertraline,
fluvoxamine,
nefazodone,
trazadone,
amitriptylene,
propanolol,
permoline,
pergolide,
gabapentin, and
bromocriptine mesylate;

with lecithin to form a therapeutic mixture.

METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS

ABSTRACT

A method and composition for transdermal delivery of psychopharmaceuticals is provided. The psychopharmaceuticals are delivered using a matrix of a lecithin gel such as a lecithin organogel. A number of psychopharmaceuticals can be used including citalopram, fluoxetine, buproprion, reboxetine, carbamazepine, valproic acid, sertraline, fluvoxamine, nefazodone, trazadone, amitriptylene, propanolol, permoline, pergolide and bromocriptine mesylate.

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VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(b)) - INDEPENDENT INVENTOR

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled "METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS", and identified as Attorney File No. 3742-903PROV, described in the specification filed herewith.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

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FULL NAME Pharmaceutical Applications Associates LLC
ADDRESS 402 East Yakima Avenue, Suite 330, Yakima, Washington 98901-2760
[ ] INDIVIDUAL [x] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: Oct. 28, 1998 By: C. Donald Williams
C. Donald Williams

Date: Oct 28, 1998 By: Robert W Murdock
Robert Murdock

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am an official empowered to act on behalf of the small business concern, Pharmaceutical Applications Associates, LLC of 402 East Yakima Avenue, Suite 330, Yakima, Washington 98901-2760.

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled "METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS" and identified as Attorney File No. 3742-903PROV, described in the specification filed herewith.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9 or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: Oct. 28, 1998

By: C. Donald Williams

C. Donald Williams
President
Pharmaceutical Applications Associates LLC

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